



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2015-N-3275]

Labeling Lower-Dose Estrogen-Alone Products for Symptoms of Vulvar and Vaginal Atrophy

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of public meeting; request for comments.

SUMMARY: The Food and Drug Administration (FDA) is announcing a public meeting and an opportunity for public comment on the topic of the labeling for lower-dose estrogen products delivered vaginally, intended to treat moderate to severe symptoms of vulvar and vaginal atrophy (VVA) due to menopause. Lower-dose estrogen products means products that contain less than the 0.625 milligrams (mg) of conjugated estrogens used in the Women's Health Initiative Study, and estradiol products containing 0.0375 mg and below. Lower-dose estrogen products are now approved for the treatment of moderate to severe symptoms of VVA due to menopause, and some in the scientific/medical community have questioned whether the current "Boxed Warnings" section in the labeling is applicable in whole or in part to these lower-dose estrogen products. This meeting, a scientific workshop, will provide an opportunity for FDA to seek input from experts on the Boxed Warnings section, estrogen exposure data, and pharmacokinetic (PK)/pharmacodynamic (PD) relationships relative to labeling lower-dose estrogen-alone products intended to treat moderate to severe symptoms of VVA due to menopause.

DATES: The public meeting will be held on November 10, 2015, from 8:30 a.m. to 5 p.m.

Registration to attend the meeting must be received by October 16, 2015, with onsite registration available between 7 a.m. and 8 a.m. the day of the meeting. See the SUPPLEMENTARY INFORMATION section for information on how to register for this meeting. Submit either electronic or written comments by October 16, 2015.

ADDRESSES: The meeting will be held at the FDA White Oak Campus, 10903 New Hampshire Ave., Bldg. 31 Conference Center, Section A of the Great Room (rm. 1503), Silver Spring, MD 20993. Entrance for the public meeting participants (non-FDA employees) is through Building 1, where routine security check procedures will be performed. For more information on parking and security procedures, please refer to

<http://www.fda.gov/AboutFDA/WorkingatFDA/BuildingsandFacilities/WhiteOakCampusInformation/ucm241740.htm>.

Submit electronic comments to [www.regulations.gov](http://www.regulations.gov). Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number found in brackets in the heading of this document.

FDA will post the agenda approximately 5 days before the meeting at <http://www.fda.gov/Drugs/NewsEvents/ucm459690.htm>.

FOR FURTHER INFORMATION CONTACT: Kimberly Shiley, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 5377, Silver Spring, MD 20993, 301-796-2117, email: [Kimberly.Shiley@fda.hhs.gov](mailto:Kimberly.Shiley@fda.hhs.gov).

SUPPLEMENTARY INFORMATION:

## I. Introduction

The loss of ovarian function with menopause leads to a drastic reduction in circulating estrogen concentration, which in turn leads to physiologic changes to the vulva, vagina, and lower urinary tract. Reduced circulating estrogen concentration results in an increase in vaginal pH, a thinning and reduction of the folds of the vaginal lining, reduction of vaginal secretions, and loss of elasticity in vaginal tissues. Symptoms of decreased circulating estrogen include vaginal and vulvar itching and/or irritation, vaginal dryness and vaginal pain (dyspareunia), and/or bleeding with intercourse. Not all postmenopausal women have symptoms of VVA that require treatment, but some women (particularly those 5 to 10 years postmenopausal), when asked, will report one or more of the above symptoms, which they deem to be bothersome and self-categorize as moderate to severe in intensity. To date, the Agency has approved estrogen products (both estrogen-alone and estrogen plus progestin) for the indications of “treatment of moderate to severe vaginal dryness, a symptom of vulvar and vaginal atrophy due to menopause” and “treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to menopause.”

Estrogen-alone products have Boxed Warnings stating:

(1) There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogen;

(2) estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia;

(3) an increased risk of stroke and deep vein thrombosis was reported in the Women’s Health Initiative (WHI) estrogen-alone substudy; and

(4) an increased risk of probable dementia in postmenopausal women 65 years of age and older was reported in WHI Memory Study (WHIMS) estrogen-alone ancillary study.

The WHI estrogen-alone studies evaluated only a single estrogen dose consisting of 0.625 mg of conjugated estrogen. As lower-dose estrogen products are now approved for the treatment of moderate to severe symptoms of VVA due to menopause, some in the scientific/medical community have questioned whether these statements in the Boxed Warning section are applicable in whole or in part to the lower-dose estrogen products.

## II. Discussion Topics

The scientific workshop on November 10th will include discussions of scientific challenges related to the following topics:

- The relevance to lower-dose estrogen products of the Boxed Warnings related to the WHI findings that: (1) Estrogens should not be used for the prevention of cardiovascular disease or dementia, (2) there is an increased risk of stroke and deep vein thrombosis in women treated with estrogen-alone, and (3) there is an increased risk of probable dementia in postmenopausal women 65 years of age and older treated with estrogen-alone.
- How to educate prescribers on the interpretation of estrogen exposure data across various estrogen dosage forms indicated for treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause. Presentation of basic PK and clinical pharmacology data concepts and an informed framework for comparing various estrogen products for prescribing purposes.
- Discuss the level of available data supporting that a given estrogen serum concentration is or is not related to adverse outcomes (for example, pulmonary emboli, deep venous thrombosis, and myocardial infarction).

- Presentation and discussion of PD biomarkers for thrombosis. Presentation of a comparison of metabolic profiles from various products, key clotting factors responsible for thrombosis, and PK/PD relationships.

### III. Meeting Attendance and Participation

If you wish to attend this meeting, email [FDAVVAworkshop@fda.hhs.gov](mailto:FDAVVAworkshop@fda.hhs.gov).

Please register by October 16, 2015. Those who are unable to attend the meeting in person can register to view a live Webcast of the meeting. You will be asked to indicate in your registration whether you plan to attend in person or via the Webcast. Your registration should also contain your complete contact information, including name, title, affiliation, address, email address, and telephone number.

Seating will be limited, so early registration is recommended. Registration is free and will be on a first-come, first-served basis. However, FDA may limit the number of participants from each organization based on space limitations. Registrants will receive confirmation once they have been accepted. Onsite registration on the day of the meeting will be based on space availability. If you need special accommodations because of disability, please contact Kimberly Shiley (see FOR FURTHER INFORMATION CONTACT) at least 7 days before the meeting.

FDA will hold an open public comment session during the November 10th public meeting to give the public an opportunity to comment. Register for this session at [FDAVVAworkshop@fda.hhs.gov](mailto:FDAVVAworkshop@fda.hhs.gov) by October 16, 2015. Additional registration will occur at the registration desk on the day of the meeting on a first-come, first-served basis if there is still time available during this session.

Docket Comments: Regardless of attendance at the meeting, you can submit electronic or written comments, including responses to the public docket (see ADDRESSES), by October

16, 2015. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at

<http://www.regulations.gov>.

Transcripts: Transcripts for the November 10th meeting will be posted, when available, at <http://www.fda.gov/Drugs/NewsEvents/ucm401167.htm>.

Dated: September 22, 2015.

Leslie Kux,

Associate Commissioner for Policy.

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